REMARKS

Claims 1, 2, 4, 16, 18, 21, 22 and 40 are currently under examination. Claim 40 is amended herein to recite "the antiangiogenic protein" instead of "angiogenic protein," thus correcting an inadvertent typographical error. Claims 2, 4 and 21 are amended herein to depend from claim 40. Support for this amendment can be found in the claims as filed and throughout the specification. No new matter is believed to be added by these amendments. Also, because the claim amendments do not include any limitations not previously considered in this case, they raise no new issues. Therefore, pursuant to the following remarks, Applicants respectfully request entry of these amendments and allowance of the claims to issue.

Applicants gratefully acknowledge the courtesy of a telephonic interview between Examiner Burkhart and Applicants' representatives, Gwen Spratt and Lizette Fernandez, on April 25, 2007. During this interview, the rejection under 35 U.S.C. § 102(b) was discussed.

Rejection Under 35 U.S.C. § 102(b)

The Office Action states that claims 1, 2, 18, 21 and 22 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Restifo et al. (U.S. Patent No. 5,733,548, March 1998) as evidenced by Tandle et al. (J. Trans. Med., 2004).

Claim 1 is canceled herein, thus rendering this rejection moot as it pertains to this claim. As confirmed by Examiner Burkhart in a telephonic interview with Applicants' representative, Lizette Fernandez, on April 25, 2007, claim 40 is not subject to the rejection under 35 U.S.C. § 102(b). As amended herein, claims 2, 18, 21 and 22 now depend either directly or indirectly from claim 40, which is not anticipated by Restifo et al. Therefore, Applicants believe this rejection has been overcome as it pertains to claims 2, 18, 21 and 22, and respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 103(a)

The Office Action states that claims 1, 2, 4, 16, 18, 21, 22 and 40 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Li et al. (US Patent No. 6,638,502) in view of Restifo et al. for reasons of record.

On page 4 of the Office Action, the Examiner has responded to Applicants' arguments by stating that Restifo et al. indicate the signal sequence may precede another peptide from 5 to 1000 amino acid residues (column 4, lines 32-40). The Office Action also states that prior art is presumed to be enabling, absent evidence to the contrary and that Applicants present no reasoning or evidence as to why expression of a heterologous polypeptide using the E19 signal sequence as taught by Restifo et al. would be unexpected. Further stated in the Office Action is that the signal sequence naturally directs the expression of a 19kD protein (hence the name E19). The Office Action also states that Li et al. allegedly teaches a signal sequence to direct the secretion of antiangiogenic proteins expressed from the adenoviral vectors, one of which, angiostatin, targets endothelial cells. Furthermore, according to the Office Action, the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of the protein and prevented tumor establishment and growth (Griscelli et al. 1998, PNAS, see in particular page 6371, first column, first full ¶).

As stated above, claim 1 is canceled herein. Claims 2, 18, 21 and 22 now depend either directly or indirectly from claim 40 Applicants reiterate that there is no motivation to combine Restifo et al. (US Patent No. 5,733,548) with Li et al. (U.S. Patent No. 6,638,502) because Restifo et al. discloses administration of a P1A tumor peptide (SEQ ID NO: 6 (9 amino acids)) linked to an adenoviral E19 signal sequence in order to induce an immune response and Li et al. discloses intratumoral administration of an adenoviral vector that expresses endostatin (185 amino acids). There is no indication in either reference that the delivery system of Restifo et al. could deliver a much larger antiangiogenic protein, such as endostatin. Therefore, there is no motivation to combine Restifo et al. with Li et al.

In response to the Examiner's assertion that Restifo et al. indicates that a signal sequence may precede another peptide from 5 to 1000 amino acid residues, Applicants respectfully point

out that setting forth a generic suggestion that an E19 signal sequence can drive expression and secretion of a peptide from 5 to 1000 amino acids does not provide any reasonable expectation that an E19 signal sequence could drive expression of a specific type of protein, i.e., an antiangiogenic protein that targets endothelial cells, that results in increased circulating levels of the antiangiogenic protein in order to achieve antiangiogenic activity via systemic administration, particularly when the only example set forth by Li et al. was a small peptide. In fact, since Restifo et al. is not a scientific publication, and because the claims issued in Restifo et al. do not include the cited range, there is no presumption that the scope of cited range has scientific validity for any protein other than E19 and a 9-mer peptide, much less the specific types of proteins covered by the present claims. A reference is considered enabling if it includes a scientific basis for what it states. In this case, there is no such scientific basis, so a presumption of validity does not apply. The standard for obviousness is whether one of ordinary skill would have had a reasonable expectation of success. One of ordinary skill would be a peer in this scientific field. This unsupported assertion in Restifo et al. would not be considered by one of ordinary skill to provide a reasonable expectation for successfully expressing other proteins.

Although the Examiner has pointed out that the adenoviral E19 signal sequence naturally directs expression of a 19kD protein, this merely confirms the normal role of an E19 signal sequence in directing expression of an adenoviral protein and in no way suggests that a non-adenoviral heterologous protein, i.e., an antiangiogenic protein that targets endothelial cells, can be expressed utilizing an E19 signal sequence at sufficiently high levels to achieve antiangiogenic activity via systemic administration. Simply because an E19 signal sequence drives expression of the protein to which it is naturally operatively linked, no matter how large that protein may be, does not mean that an E19 signal sequence can drive expression of an antiangiogenic protein to obtain levels of expression that result in sufficient antiangiogenic activity to treat tumors via systemic delivery. Even if one of skill were motivated to combine the teachings of Restifo et al. with Li et al. (and they were not), there would be no reasonable expectation that the results obtained by Applicants with the claimed compositions could be achieved.

In response to the Examiner's allegation that Li et al. clearly teaches a signal sequence to direct the secretion of antiangiogenic proteins expressed from adenoviral vectors, one of which is angiostatin, Applicants respectfully point out that the signal sequence utilized by Li et al. is a plasminogen signal sequence, and not an adenoviral signal sequence. Furthermore, angiostatin is the N terminal fragment of human plasminogen. Therefore, the plasminogen signal sequence is being utilized to drive expression of a sequence that is naturally operatively linked to a plasminogen signal sequence, i.e. the N terminal fragment of plasminogen. There is no indication in Li et al. that any signal sequence other than the signal sequence naturally associated with a plasminogen sequence would result in the expression of angiostatin, much less that a different signal sequence could be used to produce increased circulating levels of angiostatin or any other antioangiogenic protein in order to treat tumors via systemic delivery . Therefore, it cannot be assumed that the results achieved with one signal sequence, that has a specific relationship with the antiangiogenic protein, can be substituted with any other signal sequence to achieve the same results.

As stated above, the Examiner has cited Griscelli et al. as a reference showing that the systemic administration of an adenovirus expressing plasminogen (secreted by the plasminogen leader sequence) delivered high levels of protein and prevented tumor establishment and growth. Applicants respectfully point out that, like Li et al., Griscelli et al. actually utilized adenoviral constructs that expressed angiostatin K3, which is the N-terminal fragment of plasminogen. Therefore, the signal sequence utilized by Griscelli et al. is a plasminogen signal sequence, and not an adenoviral signal sequence. It is clear that the plasminogen signal sequence is being utilized to drive expression of a plasminogen sequence that is naturally operatively linked to a plasminogen signal sequence. There is no indication in Griscelli et al. that any signal sequence other than the signal sequence naturally associated with a plasminogen sequence would result in the expression of angiostatin, much less that a different signal sequence could be used to produce increased circulating levels of angiostatin in order to treat tumors via systemic delivery. Therefore, one of skill in the art, upon reading either Li et al. or Griscelli et al. would immediately recognize that in order to achieve expression of an antiangiogenic protein, a signal sequence that naturally drives expression of that sequence (e.g., angiostatin) should be utilized in order to achieve local (Li et al.) or systemic delivery of angiostatin (Griscelli et al.). Given that

the combination of a signal sequence driving expression of the antiangiogenic protein with which it is naturally operably linked was successful, one of skill in the art would not look to alter this combination by utilizing any other signal sequence, much less the signal sequence of Restifo et al., that was not naturally operatively linked to any anti-angiogenic protein. Even if one of skill in the art were motivated to do so, there was no reasonable expectation that a nucleic acid encoding an antiangiogenic protein operatively linked to an adenovirus signal sequence would have the properties of the claimed compositions, i.e. 1) the ability to increase circulating levels of an antiangiogenic protein; and 2) the ability to treat tumors via systemic delivery.

For the reasons set forth above, Applicants believe that claims 2, 4, 16, 18, 21, 22 and 40 are unobvious over Li et al. in view of Restifo et al. Thus, Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112

The Office Action states that claim 40 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for not having sufficient antecedent basis for "the angiogenic protein."

Claim 40 is amended herein to recite "the antiangiogenic protein" instead of "the angiogenic protein." Therefore, Applicants believe this rejection has been overcome and respectfully request its withdrawal.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of **$1,520.00** ($500.00 representing the Notice of Appeal fee for a large entity under 37 C.F.R. § 41.20(b)(1) and $1,020.00 representing the fee for extension of time (3 months) for a large entity under 37 C.F.R. § 1.17(a)(3)), a Notice of Appeal and Request for Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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